UCLouvain

Faculté de santé publique

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Mémoire réalisé par

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Master en sciences de la santé publique, finalité spécialisée

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Remerciements

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Le plagiat

Je déclare sur l'honneur que ce mémoire a été écrit de ma plume, sans avoir sollicité d'aide extérieure illicite, qu'il n'est pas la reprise d'un travail présenté dans une autre institution pour évaluation, et qu'il n'a jamais été publié, en tout ou en partie.

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Table of Abbreviations

ALS	*Amyotrophic Lateral Sclerosis*
sALS	*Sporadic Amyotrophic Lateral Sclerosis*
fALS	*Familiar Amyotrophic Lateral Sclerosis*
BNMDR	*Belgian Neuromuscular Disease Registry*
WHO	*World Health Organization*
INLA	*Integrated Nested Laplace Approximation*
SPDE	*Stochastic Partial Differential Equations*
SES	*Socio-Economic Status*
CI	*Confidence Interval*
OR	*Odds Ratio*

Abstract

Background

Recent research suggests that amyotrophic lateral sclerosis (ALS) might be explained by a complex interaction between environmental and genetic risk factors. We hypothesized that exposure to airborne pollutants (PM_{10}, $PM_{2.5}$, NO_x, NO_2, SO_2, O_3) could have an impact on ALS. Furthermore, we investigated the effect of this exposure on the ALS survival.

Objectives

The major objective of this study is to provide insight into the effects of air pollution on ALS.

Methods

We performed post-hoc matching of 194 cases and 598 controls with a 1:3 ratio. We estimated PM_{10}, $PM_{2.5}$, NO_x, NO_2, SO_2, and O_3 mean annual concentrations at the residential addresses of cases and controls. To assess the link between environmental exposure and disease we used a conditional logistic model that was adjusted for socio-economic status.

Results

We observed that higher odds of ALS were associated with exposure to NO_x>10 μg/m³ (OR=1.400, 95%CI: 1.012, 11.660), PM_{10} >25 μg/m³ (OR=1.409, 95%CI: 0.859, 2.310), O_3>40 μg/m³ (OR=3.027, 95%CI: 2.031, 4.512) and NO_2>20 μg/m³ (OR=1.064, 95%CI: 0.729, 1.551). Interestingly, air pollutant concentrations were higher among ALS patients compared to controls. Finally, we did not observe a significant difference in exposure concentrations between patients who survived less than two years upon diagnosis and those who lived longer ($p_{values} > 0.05$).

Discussion

This case-control study provides further evidence that exposure to air pollution is associated with higher odds of ALS. We add evidence to the effects of pollution on neurodegenerative diseases. Therefore, we believe that regulatory interventions aiming to decrease air pollutants emissions would help the primary prevention of sporadic ALS.

1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by the progressive loss of lower and upper motor neurons, thereby inducing motor weakness and muscle atrophy. [1,2] Patients diagnosed with ALS usually die within 3-5 years, mostly from respiratory complications. [3,4] To date, no curative treatment is available, [5,6] and the diagnostic delay after symptoms onset is often up to one year.[7]

ALS remains a disease without a specific diagnostic test.[6] Diagnosis criteria include lower and upper motor neuron degeneration, demonstrated by clinical and electrophysiological examination. [7] Although these criteria were first established in 1994, new diagnostic criteria are gradually being implemented and, as a result, clinicians are diagnosing more and more cases each year, contributing to the increase in incidence. [6]

The onset of the early symptoms varies from person to person and depends on the affected neurons. However, hand clumsiness and leg weakness are, in most cases, the first signs that later evolve and spread to the rest of the body. Gradually, muscles become weaker and weaker, leading to the later stages of the illness. [4] The clinical feature of muscle weakness typically starts in the limb, generally from distal muscles. Nevertheless, a bulbar onset is the starting feature in about 25% of cases. Moreover, in 10-15% of patients, a frontotemporal dementia causes behavioral changes and impairment of executive functioning. [6]

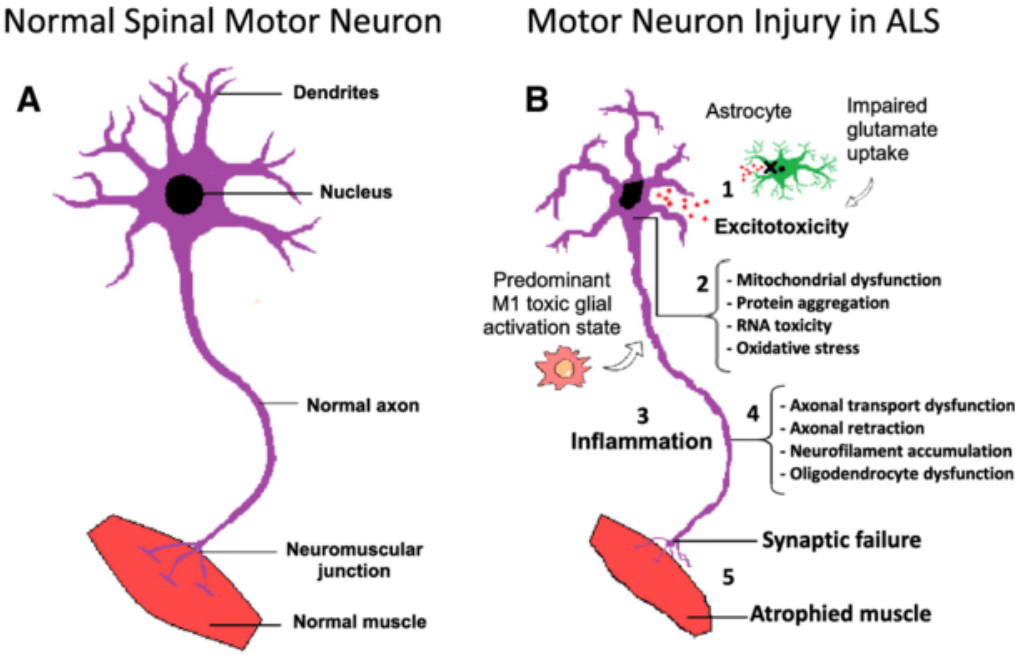

Figure 1 Molecular mechanisms in the pathology of amyotrophic lateral sclerosis. Source:[2]

Over the past decade, the number of reported amyotrophic lateral sclerosis cases has increased throughout the world. [8,9] While the prevalence is estimated between 4.1 and 8.4 per 100000 persons worldwide, the incidence ranges from 2.1 to 3.8 per 100000 persons per year in Europe. [9] These numbers thus reveal ALS as an important public health issue. [10]

Amyotrophic lateral sclerosis can be either sporadic (90%) or familiar (10%). While more than 20 genes have been linked to familiar ALS (fALS), [11] little is known about the etiology of the sporadic cases (sALS).[12] However, recent research suggests that the sporadic form might be explained by a complex interaction between environmental and genetic risk factors. [13,14] Among them, tobacco smoking, body mass index, [15,16] history of physical trauma or injury, exposure to heavy metals, organic chemicals and ultrafine air particles due to pollution have already been consistently identified. [17]

Additionally, exposure to heavy metals and organic chemicals has been linked to occupational status. For instance, it has been reported that farmers are in at-risk occupations due to their contact with pesticides involved in the etiopathology of the disease. [18,19,20,21,22] Moreover physical trauma is often associated with sports habits, whilst tobacco smoke is generally linked to individual lifestyle. [15,16]

Among the aforementioned environmental factors, exposure to air pollution is the least studied. Pollution is a source of morbidity and mortality, causing stroke, heart disease, chronic obstructive pulmonary disease, and other respiratory diseases. [23,24] Specifically, air pollution is a mixture of chemical, physical and biological particles that contaminate the environment and change atmospheric conditions.[23] The main pollutants are fine particles such as $PM_{2.5}$, PM_{25} and PM_{10}, but also gases such as CO_2, NO, CO, NO_2, SO_2 ,and NO_x. [25] Indeed, the use of fossil fuels, pesticides, and other forms of pollutants has further contributed to higher pollutant emissions. [24]

Interestingly, air pollution is known to induce oxidative stress, autophagy, apoptosis, and DNA damage in cells. [26] These effects are highly damaging for cellular organelles and proteins. Furthermore, recent studies suggest that ultrafine air particles ($PM_{2.5}$, PM_{25}, PM_{10}, PM_{coarse}) might be involved in the molecular pathways of neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's disease, and Paget's bone disease. [26,27,28]

To our knowledge, only three other previous epidemiological studies have investigated the link between exposure to air pollution and amyotrophic lateral sclerosis. [13,12,29] According to Malek et al., who conducted a case-control study with 51 sporadic ALS patients, hazardous air pollutants are involved in the pathogenesis of ALS. [12] Similarly, Seleen et al. in a populational study with 917 cases and 2662 controls concluded that traffic-related air pollutants

could have an effect on ALS. [13] Finally, Myung et al. concluded that exposure to air pollutants might also have an impact on emergency department visits amongst patients diagnosed with ALS. [30] In fact, even though mean life expectancy upon diagnosis is 3-5 years, [31] some patients survive longer and 5-10% live up to 10 years or more.[32,33]

A multidisciplinary approach has been reported in recent studies as a tool to provide better quality support to the patient and the family. The multidisciplinary team includes physicians (such as pulmonologists and neurologists), but also psychologists, nurses, nutritionists, and dentists.[17]

The establishment of comprehensive care thus makes it possible to assist ALS patients in all aspects of their daily lives, thereby increasing their quality of life and life expectancy (figure 2). [33] Understanding what factors may influence the disease progression is therefore a key step to improve ALS patients survival rate and life quality. [30]

Figure 2 Representation of the multidisciplinary approach for a person with ALS. The team should include neurologists, nursing professionals, mental health professionals, respiratory therapists, physical therapists, occupational therapists, dietitians, speech-language pathologists, social workers, etc. Source: [34]

However, to date, no study has investigated the effects of air pollution on the time survived with ALS. Moreover, we are the first to ascertain the impact of exposure to air pollution in ALS patients using Integrated Nested Laplace Approximation (INLA) and data from the European Environment Agency. [35]

The major objective of this study is therefore to provide insight on the effects of air pollution on ALS. In fact, we hypothesized that exposure to airborne pollutants (PM_{10}, $PM_{2.5}$, NO_x, NO_2, SO_2, O_3) might have an impact on amyotrophic lateral sclerosis. Furthermore, we investigated the effect of this exposure on the survival of ALS patients.

2. Methods

2.1. Study population

Our hospital is part of a network of seven neuromuscular reference centers spread throughout the country. It is important to note that in Belgium, patients diagnosed with ALS are encouraged to register with one of the seven centers, which then transmits the information to the Institute of Public Health (Sciensano). This allows to benefit from a multidisciplinary follow-up. Sciensano then centralizes the data through the Belgian Neuromuscular Disease Registry (BNMDR). [36] Currently, 1837 cases are registered in the BNMDR, of which 1464 reside in Flanders and the remaining 364 in the French speaking region. Patients followed in our hospital therefore represent 80.7% of the French-speaking region. [37]

We analyzed medical records of 294 patients diagnosed with ALS between 1999 and 2021 at *Cliniques Universitaires Saint Luc*. Criteria for selecting cases were as follows:

1) patients diagnosed with sporadic ALS
2) patients living in Belgium for at least five years previous to diagnosis
3) patients without genetic mutations, no familial history of ALS nor other neurodegenerative diseases.

Of the 294 cases initially selected for this study, 250 met the inclusion criteria. After post-hoc matching with controls (ratio = 1:3), 194 patients were retained for the final analysis (see Figure 3).

Controls were selected from the patient registry of the Sleep Center in the Pneumology unit. A total of 1050 controls were initially screened, of whom 975 met inclusion criteria. Eligibility criteria required controls to be free of ALS or other neurodegenerative disease and, living in Belgium for at least five years. Of the 975 eligible individuals, 598 controls were selected after post-hoc matching.

The following data were collected for patients:

- address (by postal code)
- sex
- age
- age at first symptoms
- age at diagnosis
- years lived with the disease
- past medical history

We then performed post-hoc matching of cases and controls with Python 3 SPSS plug-in.

Ethical approval was obtained from the institutional board of *UCLouvain* and *Cliniques Universitaires St Luc* (reference number 2021/15NOV/472). The postal codes of each patient were geocoded and transformed into geospatial coordinates. Once all the information was gathered, we pseudonymized the sample by assigning a random number to each patient. The dataset was encoded in a .csv file and a password secured access to the data. The file was then saved in the institutional cloud to provide further security.

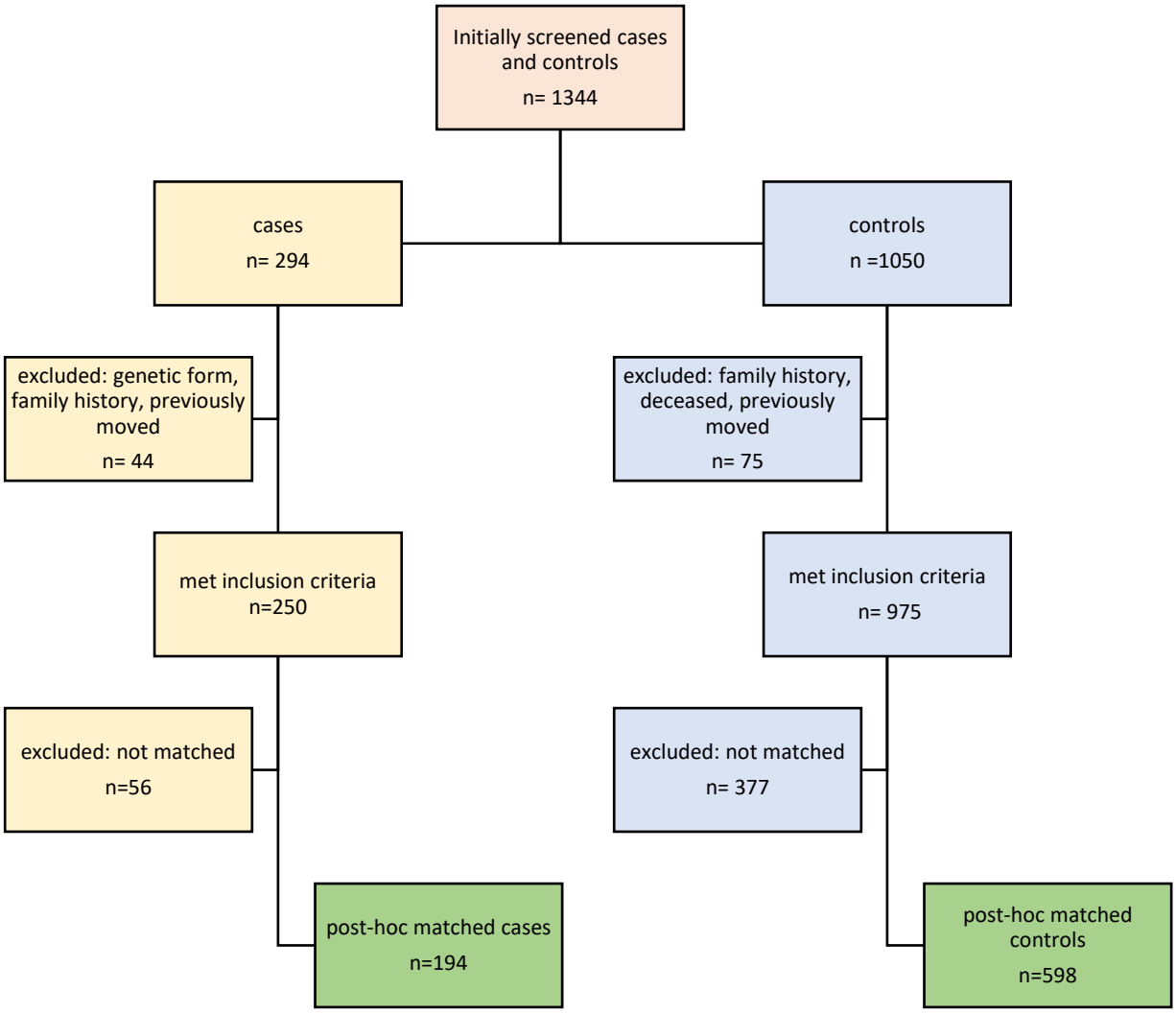

Figure 3 Flow chart of the study. Visualization of the process followed to select patients for the final analysis

2.2. Statistical analysis

We assessed environmental exposure to air pollutants using a geostatistical computational approach. The model was fitted with the Integrated Nested Laplace Approximation (INLA) in combination with Stochastic Partial Differential equations (SPDE). [38,39,40] Specifically, we used the R package INLA (version 4.0.2).

INLA is a deterministic Bayesian approach, developed as an alternative to avoid long computational times in spatiotemporal data. [38] This method estimates posterior values of variables by using prior data on recorded information.[39]

We therefore estimated PM_{10}, $PM_{2.5}$, NO_x, NO_2, SO_2 and O_3 mean annual concentrations for each case and control included in the study. [40] The estimations were based on air pollution measurements at monitoring stations derived from the European Environment Agency between 1997 and 2020. [41]

Subsequently, we subdivided the estimated concentrations into intervals. This allowed to visualize the exposure limits at which higher odds of ALS could be observed. The applied cut-offs were based on controls mean values and WHO annual international recommendations. [35]

Specifically, the following ranges were established:

1) for PM_{10} and $PM_{2.5}$

$Q_1 < 15\ \mu g/m^3$, $15\ \mu g/m^3 < Q_2 < 20\ \mu g/m^3$, $20\ \mu g/m^3 < Q_3 < 25\ \mu g/m^3$, $Q4 > 25\ \mu g/m^3$;

2) for NO_x

$Q_1 < 8\ \mu g/m^3$, $8\ \mu g/m^3 < Q_2 < 9\ \mu g/m^3$, $9\ \mu g/m^3 < Q_3 < 10\ \mu g/m^3$, $Q_4 > 10\ \mu g/m^3$;

3) for NO_2

$Q_1 < 20\ \mu g/m^3$, $20\ \mu g/m^3 < Q_2 < 30\ \mu g/m^3$, $30\ \mu g/m^3 < Q_3 < 40\ \mu g/m^3$, $Q_4 > 40\ \mu g/m^3$;

4) for SO_2

$Q_1 < 1\ \mu g/m^3$, $1\ \mu g/m^3 < Q_2 < 3\ \mu g/m^3$, $3\ \mu g/m^3 < Q_3 < 4\ \mu g/m^3$, $Q_4 > 4\ \mu g/m^3$;

5) for Ozone

$Q_1 < 40\ \mu g/m^3$, $40\ \mu g/m^3 < Q_2 < 45\ \mu g/m^3$, $45\ \mu g/m^3 < Q_3 < 50\ \mu g/m^3$, $Q_4 > 50\ \mu g/m^3$

We then assessed the link between environmental exposure to pollutants and the outcome of amyotrophic lateral sclerosis. Conditional logistic regression was therefore applied.[42]

Two models were developed: the former with unadjusted parameters and the latter with adjustment for socio-economic status (SES). Socio-economic status for cases and controls was calculated using prosperity indexes. [43]

In fact, in Belgium each postal code can be linked to a specific prosperity index. We therefore associated the postal codes for each case and control to their respective prosperity index value. We then divided the indexes into three main ranges (high SES, medium SES and low SES) based on the average income per population from the Belgian statistical office (Statbel).[43]

Additionally, the impact of exposure to pollutants on survival was analyzed based on the original 250 ALS sample. Patients were divided into two groups, with a cut-off at 2 years of survival after diagnosis. A Mann-Whitney U test was applied for the correlation analysis.

3. Results

Table 1 presents socio-economic characteristics of the studied cohort. Before matching we found that ALS patients were older and predominantly male. Medical antecedents were non-contributory in 72.9% of cases.

Since 53.2% of patients were retired, we did not include professional occupation in the analysis. Nevertheless, we observed that 18.8% of ALS patients were from a low socioeconomic background, compared with 1.1% of controls.

We therefore performed post-hoc matching with a 1:3 ratio. After matching, age, sex and socio-economic status (SES) did not differ significantly between the two groups (see Table 1).

However, cases (66.5%) and controls (65.9%) were mostly male. Moreover, the majority of matched individuals were >65 years old. Among cases, patients generally survived 2.5 years after the diagnosis and 17% were alive at the time of the data collection (see table 1).

Table 1 Socio-demographic characteristics and mean annual air pollutants concentrations of cases and controls. Results presented before and after matching

Characteristics	**Before matching**			**After matching**		
	ALS patients (n=250)	**Controls (n=975)**	**p_{value} [a]**	**ALS patients (n=194)**	**Controls (n=598)**	**p_{value} [a]**
Age (in years)	**Mean ± SD**	**Mean ±SD**		**Mean ± SD**	**Mean ±SD**	
Total	64.5± 12.3	60.9 ± 12.6	<0.001	67.4 ± 11.2	66.7 ± 10.5	0.403
Sex	**n (%)**	**n (%)**		**n (%)**	**n (%)**	
Men	142 (56.8)	739 (75.8)	<0.001	129 (66.5)	394 (65.9)	0.876
Women	108 (43.2)	236 (24.2)		65 (33.5)	204 (34.1)	
Socio-economic status[b]	**n (%)**	**n (%)**		**n (%)**	**n (%)**	
Low SES	47 (18.8)	11 (1.1)	0.486	-	-	0.107
Medium SES	87 (34.8)	573(58.8)		85 (43.8)	314 (52.5)	
High SES	116 (46.4)	391(40.1)		109 (56.2)	284 (47.5)	
Survival (in years)	**Mean ± SD**			**Mean ± SD**		
Total	2.4 ± 2.5	-	-	2.5 ± 2.6	-	-
Death	**n (%)**			**n (%)**		
Deceased	211 (84.4)	-	-	161 (83)	-	-
Alive	39 (15.6)	-	-	33 (17)	-	-

[a] *p_{values} were calculated with an independent sample t-test*

[b] *socio-economic status SES based on prosperity index*

Table 2 shows mean annual air pollutants concentrations among patients based on survival. We did not observe a significant difference in exposure concentrations between patients who survived less than two years upon diagnosis and those who lived longer ($p_{values} > 0.05$).

Table 2 Mean annual air pollution exposure for patients who survived less than two years and more than two years (n=250)

Air pollutant mean ± SD	Survival < 2 years (n= 147)	Survival > 2 years (n=103)	p_{value} [a]
PM_{10} (µg/m³)	19.9 ±2.0	20.0 ±2.1	0.539
$PM_{2.5}$ (µg/m³)	14.9 ± 1.8	15.0 ± 1.8	0.520
NO_x (µg/m³)	8.4 ± 0.3	8.3± 0.2	0.351
NO_2 (µg/m³)	23.6 ± 7.3	22.7 ± 7.2	0.275
SO_2 (µg/m³)	2.0 ± 0.7	2.0 ± 0.7	0.955
O_3 (µg/m³)	42.6 ± 3.8	42.8 ± 3.8	0.561

[a] *p_{values} were calculated with a Mann Whitney U test*

Figure 4 shows the geospatial distribution of our ALS cases in Belgium. We noted that the localization of cases is heterogeneous in the central part of the country. Patients mainly resided in Brussels and in northern Wallonia. We observed clusters around certain locations that also coincided with major traffic roads.

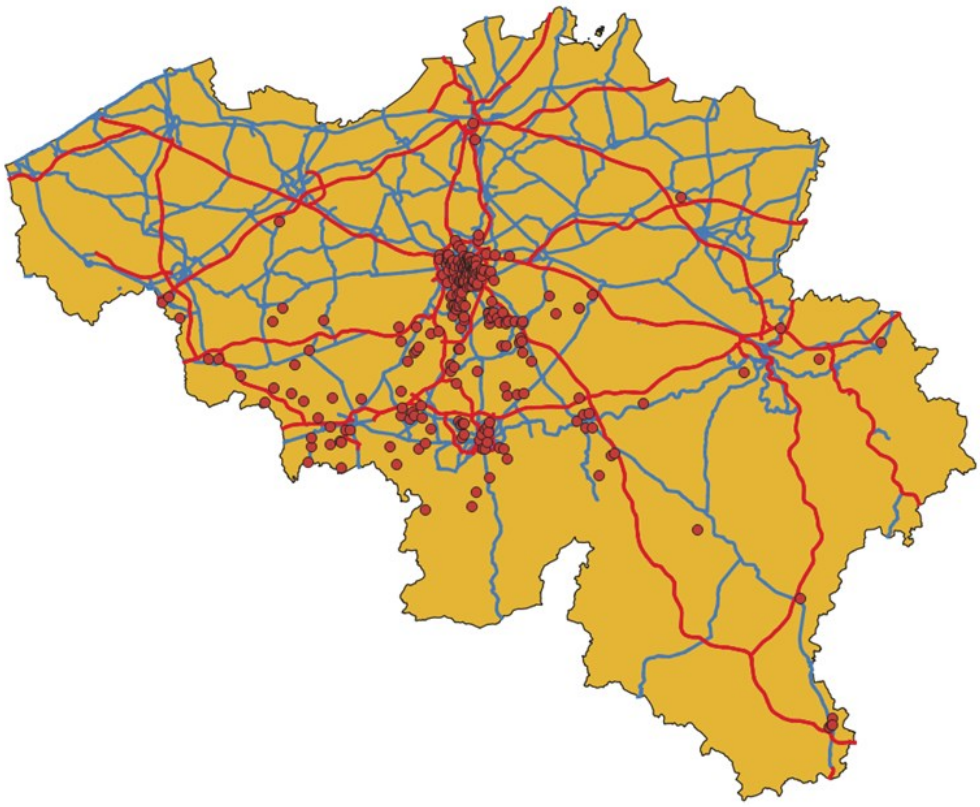

Figure 4 Geospatial distribution of Amyotrophic Lateral Sclerosis cases in Belgium. The map is based on patients followed at Cliniques Universitaires St Luc Neuromuscular Center. Major roads (blue lines) and railroads (red lines) are also depicted.

The results subsequently presented are based on 194 patients diagnosed with ALS and 598 post-hoc matched controls. Table 3 represents mean annual air pollutants concentrations for cases and controls. We observed a significant difference in exposure rates to PM_{10}, $PM_{2.5}$, NO_x, NO_2, SO_2 and O_3 between the two groups ($p_{values} > 0.05$).

Interestingly, air pollutants concentrations were higher among ALS patients compared to controls (see table 3).

Table 3 Mean annual air pollutants concentrations of cases and controls.

Characteristics	ALS patients (n=194)	Controls (n=598)	p_{value} [a]
Air pollutant (µg/m³)	**Mean ±SD**	**Mean ± SD**	
PM10	20.3 ±1.9	19.9 ±2.1	0.006
PM2.5	20.3 ± 1.9	14.9 ± 1.9	<0.0001
NOx	8.3± 0.7	8.3 ± 0.3	0.006
NO2	25.7 ± 8.0	23.0 ± 7.4	<0.0001
SO2	2.3 ± 0.6	2.0 ± 0.7	<0.0001
O3	42.8 ± 3.8	41.2 ± 4.2	<0.0001

[a] *p_{values} were calculated with an independent sample t-test*

Table 4 shows the results of the conditional logistic analysis for cases and controls. Two models were applied: model 1 was unadjusted, model 2 was adjusted for socio-economic status (SES). The results obtained with the two models followed a similar trend.

The odds ratios (ORs) of NO_x, NO_2, PM_{10} and O_3 were higher among exposed individuals in comparison with the reference category (with the lowest mean annual concentration) for both unadjusted and adjusted models.

We observed that ORs for NO_x were significantly elevated among highest exposed subjects in comparison with lowest exposed individuals.

Furthermore, our analysis showed that exposure to O_3 was associated with higher odds of ALS (OR=3.027, 95%CI: 2.031,4.512).

We did not observe a significant odds ratios related to SO_2 mean annual concentrations ($p_{value} = 0.339$). Additionally, the ORs associated with $PM_{2.5}$, although significant, were not calculated due to a lack of data concerning higher exposed quartiles.

Table 4 Conditional logistic regression model to determine the association between exposure to air pollutants and ALS.

Pollutant	Model 1 [a] OR (95% CI)	Trend p value	Model 2 [b] OR (95% CI)	Trend p value
NO_x (µg/m³)				
$[NO_x] < 8$	Reference	0.012	Reference	0.012
$8 < [NO_x] < 9$	0.423 (0.191, 0.937)		0.425 (0.191, 0.945)	
$9 < [NO_x] < 10$	0.988 (0.319, 3.059)		0.940 (0.302 2.924)	
$[NO_x] > 10$	1.383 (0.167, 11.431)		1.400 (1.012, 11.660)	
PM_{10} (µg/m³)				
$[PM_{10}] < 15$	Reference	<0.0001	Reference	<0.0001
$15 < [PM_{10}] < 20$	0.495 (0.133, 1.842)		0.520 (0.139, 1.941)	
$20 < [PM_{10}] < 25$	1.070 (0.397, 2.887)		1.108 (0.410, 2.998)	
$[PM_{10}] > 25$	1.414 (0.863, 2.316)		1.409 (0.859, 2.310)	
O_3(µg/m³)				
$[O_3] < 40$	Reference	<0.0001	Reference	<0.0001
$40 < [O_3] < 45$	3.027 (2.031, 4.512)		2.994 (2.007, 4.465)	
$45 < [O_3] < 50$	2.423 (1.591, 3.688)		2.336 (1.531, 3.565)	
$[O_3] > 50$	2.125 (0.546, 8.263)		2.126 (0.545, 8.290)	
NO_2(µg/m³)				
$[NO_2] < 20$	Reference	0.002	Reference	0.005
$20 < [NO_2] < 30$	1.800 (1.288, 2.516)		1.064 (0.729, 1.551)	
$30 < [NO_2] < 40$	1.055 (0.724, 1.537)		1.008 (0.692, 1.469)	
$[NO_2] > 40$	0.988 (0.679, 1.439)		0.530 (0.239, 1.359)	

[a] unadjusted model [b] model adjusted for SES

Figure 5 and 6 show concentration estimates for PM_{10} and O_3 between 1997 and 2020. We note that concentrations are higher around certain agglomerations. Particularly, PM_{10} estimates are elevated around Brussels (>26 μg/m³), while O_3 emissions are higher in Southern Wallonia (>55 μg/m³).

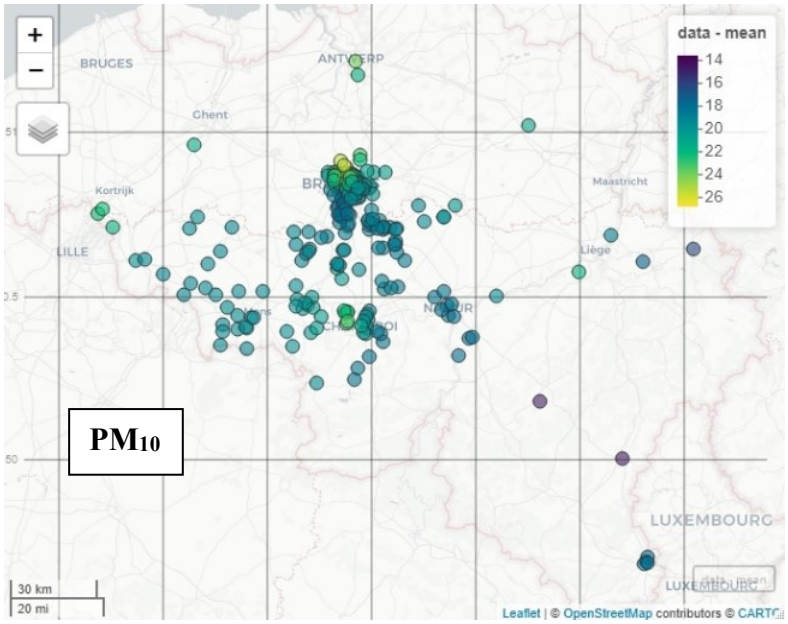

Figure 5 PM_{10} mean annual concentrations at the addressed of ALS cases between 1997 and 2020

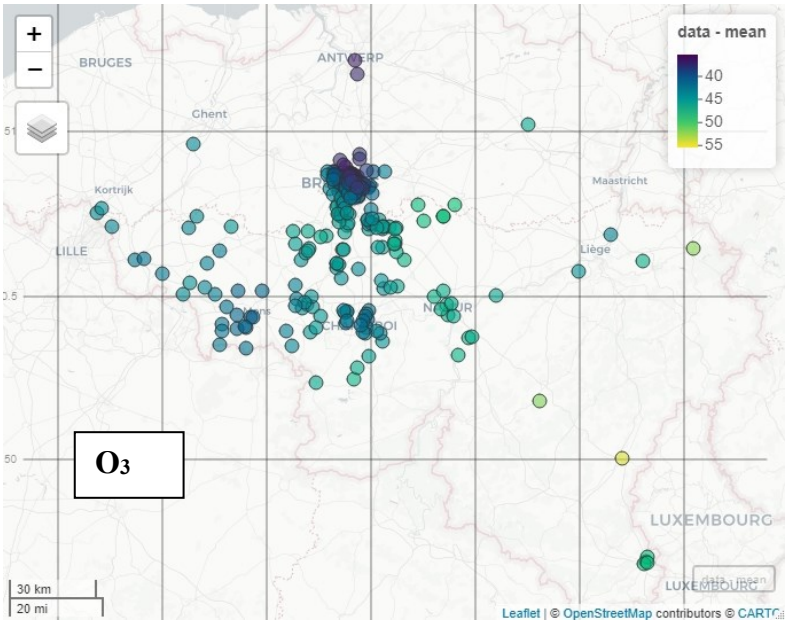

Figure 6 O_3 mean annual concentrations at the addressed of ALS cases between 1997 and 2020

4. Discussion

In this study, we focused on air pollutants exposure based on place of residence of ALS patients and controls. Interestingly, we found that exposure to air pollutants was associated with higher odds of amyotrophic lateral sclerosis.

Specifically, we noted that ozone, nitriles and particulate matters concentrations were higher for ALS cases, compared to controls. Furthermore, we observed a significant difference in exposure concentrations between the two groups (p_{value} <0,05). Our results suggested a potential correlation between air pollution and amyotrophic lateral sclerosis. In fact, we noted higher odds ratios associated with increased concentrations of PM_{10}, NO_x, NO_2 and O_3. It is important to note that gender and age distribution of cases was similar to that in the literature, [37] and our sample was representative of the overall Belgian ALS population. In addition, most of our cases and controls were from high socio-economic areas.

Among the air pollutants we hereby identified as having a correlation with ALS, PM_{10}, NO_x and NO_2 are related to road dust and traffic activity. [20,21,22] In fact, it has been reported that nitriles and particulate matters are involved in vehicle emissions. [44,45] Moreover, traffic-related emissions near busy roads have been comprehensively studied in recent years, [46,47] highlighting the influence of its exposure on many diseases. [48,49]

Interestingly, we found that major highways were located near the homes of ALS patients (figure 2). A recent systematic review showed that, in a significant number of studies, NO_x exposure was correlated to neuronal damage. [50] It has also been demonstrated that neuroinflammation and oxidative stress are key players in molecular pathways of neurodegenerative diseases and, recent research showed the effects of oxide nitriles on the overall process. [51]

Furthermore, some studies suggest that ultrafine air particles ($PM_{2.5}$, PM_{25}, PM_{10}, PM_{coarse}) are able to cross the blood-brain barrier and induce chronic brain inflammation, [12,52,53] thereby leading to neurodegenerative diseases. [28,54] Our study, which is one of the few to focus on the problem from an epidemiological perspective, further reinforces previous neurological findings.

Additionally, we found that O_3 emissions were significantly associated with higher odds of ALS. Interestingly, this specific type of pollution has previously been linked in the literature to loss of synaptic plasticity and, consequently, alterations in information processing along with

neuronal activities. [55] Ozone emissions originate from photochemical reactions following solar radiation. This contributes to the burden of disease in some of the most polluted cities around the world. [56]

The strength of our study is that it is one of the first to investigate the relationship between air pollution and ALS, based on geolocation.

Indeed, in the case-control study by Malek et al, residential addresses of sporadic ALS patients were geocoded and associated with exposure to aromatic solvents but did not investigate the effects of traffic and particulate air pollutants. [12]

Conversely, Seelen et al. used land-use regression models to estimate exposure concentrations of nitrogen oxides and particulate matter for each patient included in their study (917 patients and 2662 controls), but a potential limitation of their study was the uncertainty of the air pollutant estimates.[13]

Notwithstanding, our findings are in line with these previous studies, and we provide further proof to the effects of air pollution on amyotrophic lateral sclerosis disease course. [57]

Interestingly, recent studies have shown a possible correlation between occupational status and ALS, [58] but in the context of this study we could not elucidate this aspect due to lack of information about the profession of many participants. In fact, 53.2% of the ALS patients were retired.

A possible limitation to our study is the fact that we did not have information about the professional occupation of our sample and, therefore, we could not adjust our model to occupational exposure. Nevertheless, we used the socio-economic status as a proxy and therefore adjusted the model accordingly. Consequently, this limitation had no influence in the final interpretation.

Although recent studies suggested a correlation between ALS and short-term SO_2 exposure, [30] our results did not corroborate the previous observations. This association should thus be further investigated in future research.

Additionally, we investigated the link between ALS patients and exposure to air pollution. To our knowledge, this is the first study to analyze the impact of air pollution on the survival of ALS patients.[59] Nevertheless, our results did not show a significant correlation between being exposed to pollutants and surviving more than two years upon diagnosis ($p_{values}>0.05$). Interestingly, it has been reported that survival can be influenced by site of onset (bulbar or distal), age at diagnosis and, most importantly, use of non-invasive ventilation. [31,60]

Therefore, another limitation to our analysis is that we did not know who, amongst our patients, used non-invasive ventilation. Without this information we were not able to adjust our survival analysis. Further research is thus needed to demonstrate the association between prolonged exposure to air pollutants and survival after ALS diagnosis.

Finally, this population-based study provides further proof of the increased odds of ALS associated with exposure to air pollutants (particularly PM_{10}, NO_x, O_3 and NO_2). Our findings are therefore consistent with recent literature and, we add evidence to the adverse effects of pollution on human health.

In conclusion, to improve the quality of life of ALS patients, future research should focus not only on the underlying causes that may trigger the sporadic form but also on the factors that may accelerate or slow the progression of the disease. This would allow preventive action to be taken and extend the length and quality of life of affected patients. [30] In fact, we observed higher odds of amyotrophic lateral sclerosis well below the current European annual limits of 26 $\mu g/m^3$ for NO_x and 20 $\mu g/m^3$ for PM_{10}. [61] Therefore, we believe that regulatory interventions aiming to decrease air pollutants emissions would help the primary prevention of sporadic ALS. These regulations would furthermore improve the general wellbeing of the population.

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